REMARKS

With entry of the current amendment, clams 1 and 11 have been amended and claims 5, 12, and 27 have been cancelled. Claims 1-4, 7-11, 13, 14, 16, 17, 22-27, and 29-32 are thus pending in the application.

The rejections are addressed in the order set forth in the Office Action mailed February 12, 2003.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7-14, 22-27, and 29-32 stand rejected as allegedly lacking adequate written description. The Examiner alleges that claims 1 and 11 recite an immunoconjugate that has 95% sequence identity to SEQ ID NO:2 or SEQ ID NO:4, and that has 90% or greater of the binding affinity of the prototype RFB4dsFV. However, the Examiner has misinterpreted the claim. The claims prior to amendment clearly recite that it is the RFB4dsFV moiety of the immunoconjugates that has V_H and V_L regions with the specified identity to SEQ NO:2 or NO:4 the specified binding affinity. Thus, the claims are, in fact, supported by the passages noted in the specification. However, in order to expedite prosecution, claims 1 and 11 have been amended, thereby obviating the rejection. Applicants therefore respectfully request withdrawal of the rejection.

Applicants reserve the right to pursue the subject matter of claims 1 and 11 prior to amendment in a continuation application.

Rejections under 35 U.S.C. § 103

Claims 1-5, 7-14, 16, 17, 22-27, and 29-32 stand rejected as allegedly obvious over the cited art. The Examiner argues that one of skill in the art would have been aware of established procedures for isolating V_H and V_L genes based on hybridization and that procedures taught in the cited references would have led the artisan to have made the claimed cDNA encoding the RFB4 antibody with a reasonable expectation of success. Again, Applicants respectfully traverse. As acknowledged by the Examiner, Orlandi *et al.* teach that "our primers

might amplify most immunoglobulin mRNA of the mouse repertoire". They also teach that "it is not possible to determine the exact sequence at both ends of the V genes" (emphasis added). The Examiner indicates that this can be overcome simply by using different primers for sequencing. Orlandi *et al.*, however, suggest no such thing. They teach that the sequences at the ends reflect the primers used, *i.e.*, the sequence in this region is determined by the amplification primers. (*see, e.g.*, the legend to Figure 4 on page 3836, which states that this region of the amino acid sequences are encoded within the amplification primers). These amplification primers were designed based on alignments and inclusion of the common nucleotides at these positions. They do not reflect the sequence of any particular V_H or V_L, let alone the V_H and V_L sequences of RFB4. The disclosure additionally discusses the uncertainties in the sequence on page 1837, first paragraph. Thus, use of different sequencing primers would not solve the problem of obtaining the true sequence at the ends of a particular V_H or V_L. Accordingly, the combination of Orlandi with the other cited references would not reasonably be expected to lead to SEQ ID NO:2 and SEQ ID NO:4 as set forth in the claims.

Applicants also cited Reiter *et al.* (*Nature Biotechnology* 14:1239-1245) to support the position that the superior binding properties, *i.e.*, RFB4dsFv immunoconjugates having a binding affinity that is essentially equivalent be the binding affinity of the unconjugated RFB4 IgG, can be predicted for a specific antibody. The Examiner argues that Table 3 of Reiter clearly demonstrates that, in almost ever case, the cytotoxicity of the dsFv is better than the scFv. However, Applicants note that the binding of the dsFv immunoconjugates is equivalent to the parent IgG in only a minority of the cases. No rationale for predicting which immunoconjugates would exhibit this property is provided, either in the cited art or by the Examiner. Moreover, with regard to other anti-CD22 antibodies, *e.g.*, LL2 antibodies, the art demonstrates that one of skill in the art cannot reasonably predict which particular anti-CD22 scFv or dsFv constructs will be expressed well and exhibit significant antitumor activity. For example, Krietman and Pastan (seminars in *Cancer Biology* 6:297-306, 1995, attached as Appendix A) teach on page 303 that chemical conjugates comprising LL2 or LL2(Fab') joined to truncated PE were very cytotoxic toward Burkitt's lymphoma cell lines in cell culture and exhibited significant anti-tumor activity

in nude mice bearing solid subcutaneous Burkitt's lymphoma tumors. However, recombinant single-chain and dsFv versions of the immunotoxin were found to have low activity, believed to be due to poor association of LL2(V_H) and LL2(V_L) during renaturation. Thus, as evidenced by a close example from the art, the superior binding properties and cytotoxicity of the claimed anti-CD22 immunoconjugates are unexpected and surprising.

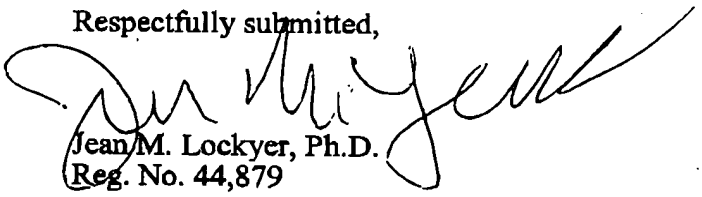
In summary, one of skill could not combine the cited reference to predict the sequences set forth in SEQ ID NO:2 and SEQ ID NO:4. Nor could the artisan predict which particular conjugate would have expression characteristics and cytotoxic properties that are characteristic of the claimed immunoconjugates. Thus, the claimed sequences are not obvious. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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